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Seek and Ye Might Find

I. Looking for Answers in Only a Few Places

There is an old joke about a man who has lost a key, which reveals much about the analysis of theories and their evolution in the philosophy of science. In the joke, a man is walking his dog down a dark street one night when he encounters his neighbor. The neighbor is on his knees under a street lamp, obviously hunting around for something on the ground. "What are you looking for?" the dogwalker asks. "I lost my house key and I am trying to find it" responds the neighbor. "Why are you looking there?" the inquisitive dogwalker asks. "Because," the neighbor responds, "that is where the light is."

I believe that philosophers of science have spent the better part of the twentieth century looking where the light is. An endless parade of philosophers of science have set out to understand the process of conceptual evolution in the sciences by looking only where the light is. They have taken as their data base almost exactly the same range of concepts, theories, and research paradigms that those in previous generations have sought to examine.

But, it might be objected, the claim that the scope of the philosophy of science has remained static cannot possibly be true. The philosophy of science has undergone a rapid expansion in the variety of scientific theories (Suppe 1977) subjected to philosophical analysis in the past few decades.

Philosophers of science once confined their analyses of conceptual evolution almost exclusively to the theories of the physical sciences. The writings of the postwar positivists devoted an extraordinary amount of attention to mechanics, thermodynamics and quantum theory (Feigl and Brodbeck 1953; Hempel 1952; Nagel 1961; Popper 1959). But today there are any number of philosophers of science interested in examining conceptual change in the biological sciences, the geological sciences, and in the various social sciences. The observational domain of the philosophy of science in the 1980s is far more extensive than was true even in the 1960s and 1970s.

Moreover, defenders of the catholicism of the present generation of philoso-

phers of science might add, the philosophy of science has discovered the history and sociology of science. Even though this discovery has spawned all manner of interdisciplinary wrangling as to which students of science have the right set of tools in hand for understanding conceptual change, the fact is that the debate has been joined (Engelhardt and Caplan 1987; Giere 1988).

The debate has forced philosophers of science to ruminate upon a much broader range of theories within the sciences than they might if left to their own devices. Since sociologists and historians have been less prone to develop obsessions with the physical sciences, the philosophy of science, if only to preserve its intellectual autonomy, has had to fish in all manner of new scientific waters.

Moreoever, there has been an expansion of the units of analysis where conceptual evolution is concerned. Where theories were once seen as the sole units of conceptual evolution, it is now widely understood that science organizes its inquiries around concepts, problems, paradigms, themata, research strategies, controversies, and exemplars (Englehardt and Caplan 1987)

Those excited by the expansion of the exemplary domain of the philosophy of science are correct. There has been a great deal of growth, for a variety of reasons, in the scientific subfields and specialities that contemporary philosophers of science are willing to examine.

But, the boundaries of philosophical reflection about science were once so limited that almost any broadening of disciplinary vision appears to be significant. If one looks more closely at the specific examples that constitute the explanatory domain of the philosophy of science today, some of the catholicity is more apparent than real.

Consider the set of prominent examples in the area of the philosophy of science that has grown more quickly than any other during the past twenty years – the philosophy of biology. Even a cursory examination of the biological theories, research strategies, and paradigms that have been discussed reveals that there is a sampling strategy in use by those in this subfield that has resulted in a very peculiar picture of the biological sciences.

If one reviews the periodical literature in the philosophy of biology by browsing through the tables of contents of those books that form the basic reference points for the field (Beckner 1968; Brandon and Burian 1984; Hull 1974; Mayr 1982; Munson 1971; Rosenberg 1985; Ruse 1973; Sober 1984), scanning dissertation topics written about the biological sciences by philosophers during the past two decades, and looking at the contributions to the major journals in the philosophy of science, it quickly becomes obvious that the philosophy of biology, with few exceptions, is in actuality either the philosophy of evolutionary biology or the philosophy of population genetics.

Darwinism and the subsequent disputes that have followed in its wake constitute one primary focus of philosophical attention. Most of the rest of the philosophy of biology's attention span is riveted on understanding the nature of the rela-

tionship that exists between three theories: Mendelian genetics, population genetics, and molecular genetics.

Admittedly evolution and genetics are significant areas of inquiry within biology. But there is more going on in biology than disputes over the plausibility of a punctuated equilibrium approach in explaining macroevolution or whether a molecular explanation can be given for either Mendel's laws or the Hardy-Weinberg law. Almost nothing has been written by philosophers of biology about ideas, theories, research programs, exemplars, and the like in such areas of the biological sciences as biochemistry, botany, developmental biology, ecology, physiology, immunology, behavioral biology, paleontology, or biogeography.

The data sample of the philosophy of biology is surprisingly sparse. But matters are even worse than this. For the angle of the street lamp that has been determining where philosophers of biology should look in order to understand conceptual evolution is very definitely skewed.

The choice of examples in the literature of the field is drawn almost exclusively from the most abstract concerns of biology. To read the examples of theories cited by philosophers of biology, one would come away with the very distinct impression that most biologists spend most of their work days driven by conceptual questions of a very general nature. In the world of biology, as presented in the periodical literature of the philosophy of biology, most biologists spend no time with living organisms, rarely venture outside the boundaries of their office or laboratory, and are driven only by a desire to concoct a single overarching theory that can answer fundamental but very abstract questions.

This is a distorted view of the state of affairs in the biological sciences. The overwhelming majority of biologists spend their time wrestling with theories, concepts, research programs, and problems in the service of practical and applied problems.

The majority of biological scientists work in schools of forestry, horticulture, veterinary science, agriculture, pharmacy, or medicine. The majority of those who think of themselves as biologists and who recognize others as doing work in biology spend their days thinking about problems, constructing theories, and refining models in conceptual terrain where nary a philosopher of biology has deigned to tread.

The avoidance of the applied in science is not a prejudice that is confined to philosophers of biology. Most other specialty fields of the philosophy of science do not pay attention to the practical or applied domains of science.

Most areas of engineering, chemistry, psychology, dentistry, nursing, nutrition, geography, architecture, pharmacy, oceanography, soil science, and metallurgy, to name some of the most obvious, remain unremarked upon by philosophers of science. The scope of the philosophy of science, while expanding, is still focused on only a tiny fraction of the domain of science in which most of those

who call themselves scientists, who are funded to do science, and whom society recognizes as scientists work.

The lack of attention to applied areas of science by philosophers of science is, to put it bluntly, systematic and thorough. Why this is so is a topic worthy of inquiry in its own right. That it is so is obvious.

This paper has a grandiose goal—to try and highlight the fact that the domain of examples governing philosophical reflection about science is highly determinative of how the conceptual evolution and change is understood and explained. The importance attributed to paradigms or exemplars in theory construction (Kuhn 1970, Kitcher 1983a, 1983b; Schaffner 1986), the pace at which theories are thought to evolve in science (Laudan 1977), the extent to which theories can be axiomatized, and the deductive or nondeductive nature of relationships between theoretical statements are closely tied to the examples of scientific theories that are selected for analysis. Similarly, the adequacy of evolutionary models of theory change, attempts to ascertain the logic of discovery (Nickles 1980), Nagelian models of theoretical reduction (Caplan 1981; Schaffner 1967; Robinson 1986) or of various views of the role of crucial experiments in science (Feyerabend 1981), all pivot on the adequacy of the data base that is used by those doing the philosophizing.

And those doing the philosophizing have shown no interest in the practical, pragmatic side of science. I believe this orientation has come at great cost in terms of a valid understanding of conceptual change.

The evidence cited in support of this claim will itself rest on a rather flimsy evidential base. I shall discuss a single example of inquiry in medicine, one drawn from the field of nephrology. The example, the development of a treatment for chronic renal failure, reveals an interesting pattern of theoretical and practical efforts to solve a pressing problem in one tiny subdomain of applied science.

The example may or may not be typical of how ideas evolve in medicine. It may or may not be typical of how ideas evolve in applied domains of science. And it may or may not be illustrative of how theory and practice coevolve to produce both stasis and change in the evolution of ideas.

But the example is certainly a valid instance of how ideas in one portion of science have evolved. And, as such, it reveals how narrow the present scope of philosophical reflection about science is and what sorts of insights might await those willing to broaden their perspective by broadening the domain of their analytical efforts.

Conceptual evolution may not be uniform in all areas of science. I remain agnostic as to whether the dream of a theory of "unified science" (Feigl and Brodbeck 1953) can be discovered. But no one will ever know unless a complete and comprehensive range of theories, concepts, research programs, paradigms, and problem-solving strategies from all domains of science is utilized in constructing the subject matter of the philosophy of science.

The philosophy of science in general, and those interested in the problem of conceptual change in the biomedical sciences in particular, are not well served by confining their attention to those places where "the street lamp is shining." Unless an argument is mounted, and to date none has been advanced, that certain areas of science are more representative, typical, paradigmatic, or illustrative of science than are others, then philosophers will have no excuse for continuing to generate analyses of conceptual change that ignore most of what is funded as, published as, and rewarded as science. The only plausible research strategy for arriving at an understanding of the dynamics of scientific change is to look at science in its entirety, not simply at those areas of science that have departments with the closest locations, physically, historically and spiritually, to philosophy departments.

II. Kidneys and Diseases of the Kidneys

The kidney is an organ that sometimes makes a cameo appearance in philosophical discussions of the life sciences. Sometimes it appears in discussions of teleological explanation, as a refutation of the claim that teleological claims can be translated without remainder into claims about causally necessary conditions for achieving a goal. Occassionally it winds up lumped with hearts, as illustrative of the kind of products natural selection has produced in various species.

But from the point of view of most scientists in biology and medicine, the kidney represents much much more than a readily comprehensible example in the ongoing dispute about the irreducibility of teleology in biological explanations. In particular, those in medicine and veterinary science have a keen interest in the function of kidneys, since when they do not function the consequences for the organism possessing them are fatal.

Death has a way of riveting the attention of those interested in physiology. Moreover, preventing death is a goal that fuels a great deal of inquiry in the biomedical sciences. The ability to restore the function of failing kidneys, or to provide a substitute for kidneys whose function has been irreversibly lost, has been a major preoccupation of biomedicine in the years since the end of the Second World War.

The kidneys' primary function is to remove waste materials from the blood. The normal metabolism of fat and carbohydrates in the human body produces on average about 70 mEq/kg each day of nonvolatile acid. An additional 13,000 mEq of carbonic acid is produced as well. If these acids are not removed, coma, shock, and heart failure will result (Fishman, et. al. 1981).

The kidney also serves important regulatory functions in terms of the maintenance of total body fluid and electrolytes. The body's pH levels are also maintained by the kidney. Since the ability of mitochondria in each cell to generate ATP through oxidative phosphorylation is a function of the pH gradient present

across the mitochondrial membrane, renal function is an absolute necessity for life.

The primary business of the kidney is performed in units called nephrons. Each kidney contains about one million. A nephron consists of two major parts.

The glomerulus is a ball of thin-walled capillaries. Blood enters the glomerulus from the renal artery. The small size of the vessels composing the glomerulus raises the pressure of flow, resulting in the filtration of fluid and solutes through the thin walls of the capillaries. This filtrate then travels through a long looping tube, the Loop of Henle, to a third element known as a tubule. Here various solutes are reabsorbed back into the blood stream. The remaining fluids and heavier solutes, now constituting urine, drain from the tubules into the bladder.

The nephrons of the kidney constitute an enormous countercurrent system. The differential permeability of the glomerulus, the Loop of Henle, and the tubule creates a cycle in which sodium ions are first actively pumped out of the blood and then, as water diffuses out, return and are excreted as concentrated salts in the form we know as urine.

A sudden loss of kidney function is termed acute renal failure. The most common cause of this condition is traumatic injury to the kidneys. But kidney failure can also result from the consumption of various toxic agents such as heavy metals, aminoglycoside antibiotics, or alchohol.

Acute renal failure can sometimes be reversed. For example, it may be possible to reverse the effects of a traumatic injury through surgical intervention. When this is not possible, a new diagnosis is applied—chronic renal failure.

The most common cause of chronic renal failure is not sudden injury or insult to the kidney. There are a number of progressive degenerative diseases that strike the kidneys and cause them to slowly fail over a period of months or years. These diseases can be classified into two forms: glomerular and interstitial.

In glomerular renal failure, the glomeruli of the kidney cannot admit blood into the kidney. This can result from hypertension, which destroys the ability of the capillaries to generate sufficient pressure to filter the blood. Or it can result from streptococcal infections, autoimmune diseases, or myelomas.

In interstitial diseases, the tubules of the kidney become inflamed and suffer fibrosis. The tubules are then incapable of permitting the exchange of salts and water between the nephron and the bloodstream. Diabetes, sickle-cell anemia, and the long-term ingestion of analgesics can cause this form of chronic renal failure.

For the first half of the twentieth century, medicine had no treatments to offer those who suffered acute or chronic renal failure. However, physiologists realized as early as the 1910s that it might be possible to mimic the function of the kidneys by creating a machine that could pump blood through a tube composed of a semipermeable membrane. If a salt solution of the proper concentration was placed on the other side of a membrane of the right thickness and composition,

waste materials should diffuse across the membrane, duplicating, to some extent, the processes by which urine is formed and removed from the body. The first "artificial" kidney was built in 1914. But the membrane used was so fragile that it could not stand up to the volumes and pressures necessary for use in human beings.

III. The Early Evolution of Hemodialysis – Solving the Problem of Circulatory Access

The first machines capable of substituting for the function of the kidneys were invented during World War II. The key breakthrough was the invention of cellophane, which was both permeable enough and sturdy enough to stand up to prolonged blood flows.

Willem Kolff built a somewhat primitive artificial kidney and performed the first "hemodialysis" in a human being in 1943. In 1956 Kolff and Watschinger introduced a new model of artificial kidney, the twin-coil dialyzer, a design still evident in many of the machines used in dialysis during the next 25 years (Czaczkes and Kaplan De-Nour 1978).

By the late 1950s several American and European medical centers had artificial kidney machines that were capable of "resting" the kidneys of persons afflicted with acute renal failure. The clinical approach was to temporarily substitute an artificial kidney for the natural kidneys in the hope that the damaged kidneys might regain their functional capacities.

The use of these machines required the insertion of tubes or cannulas into a patient's artery and vein in order to bring blood from the patient to the machine and return it to the patient. However, the amount of blood involved required the use of needles with such large bores that each treatment required the use of a new artery and vein. Physicians quickly ran out of accessible sites to a patient's circulatory system.

Physicians in the early fifties had a treatment that was efficacious for many forms of acute renal failure. But the problems associated with gaining access to the circulatory system made it impossible to use the first generation of artificial kidney machines for those with chronic renal failure.

The problem of how to gain continuous access to the circulatory system without destroying it dominated the theoretical and clinical efforts of nephrologists. In 1959 Scribner and Quinton of the University of Washington discovered a solution.

Scribner and Quinton realized (Fox and Swazey 1978) that by implanting a permanent tube, or shunt, between an artery and a vein, blood circulation in the vessels could be maintained. Yet a surgically implanted tube would permit repeated access to the circulatory system without damaging blood vessels.

The original version of the Scribner-Quinton shunt was a T-shaped plastic

tube. One end of each bar of the shunt was sewn directly onto an artery and a vein, usually in the patient's arm. When access to the circulatory system was necessary, the remaining portion of the T could be removed and the ends fed to tubes leading directly to an artificial kidney machine. By permanently short-circuiting the circulation in an artery and a vein, a permanent access site to the circulatory system could be maintained.

There was a key breakthrough in materials science that facilitated the invention of the Scribner-Quinton shunt. A new inert material, Teflon, had recently become available. Though not promoted by the manufacturer for its medical applications, Scribner realized that the smooth surface of the new substance made it unlikely that blood cells would be damaged in passing over a Teflon surface. The fact that it was inert made it a plausible material to attempt to use in the human body, since Teflon would not trigger an immunological reaction.

The Scribner-Quinton shunt, and the subsequent versions constructed of Silastic, a more flexible inert material, made it possible to treat those with chronic renal failure. With a mechanism available for maintaining access to the blood that did not destroy access sites in the process, existing artificial kidneys could be used for persons suffering from all forms of chronic renal failure.

Scribner and Quinton had made an important breakthrough with respect to renal disease. But, the discovery immediately created two new problems.

IV. Selling Is the Daughter of Invention

A problem facing those who wanted to use the shunt to try and treat patients in chronic renal failure was that no one knew what the effects would be of long-term exposure to an artificial kidney machine. No one knew how often or how long patients ought to be hemodialyzed on the artificial kidney. Nephrologists did not know whether the machines would continue to be effective over time.

Nor did they know what the side effects would be of long-term treatment using an artificial kidney. Would unfiltered impurities enter the bloodstream? Would the machine remove too many vital salts or cause other problems in patients with renal failure?

Another, more practical, problem confronted the inventors of the shunt. Now that they had concocted a solution to the problem of allowing constant access to the circulatory system, they needed to inform other doctors of their discovery.

Certainly publication was a critical element in communicating the new breakthrough and Scribner and Quinton published a number of papers on the subject of the shunt (Scribner, et. al. 1960). But publication was not enough. Physicians and especially surgeons needed to see and handle the new shunt in order to understand how it could be implanted and what opportunities it might create. Having invented a shunt, the inventors had to let others see and manipulate the invention in order to demonstrate its practicality and utility.

Scribner and Quinton spent roughly three years, from 1959 to 1962, disseminating their ideas concerning the opportunities offered by a permanently implanted shunt to other nephrologists. Scribner made presentations at many medical meetings. He brought samples of his shunt with him to show to his peers sometimes during coffee breaks, or in his hotel room.

Many physicians, particularly younger doctors interested in renal failure, showed an interest in the shunt. A number of physicians went to Seattle to do residencies with Scribner in order to learn how to implant the shunt (Rettig 1976).

V. Moving from Skepticism to Acceptance

The sales efforts and training programs of Scribner and his colleagues paid dividends. In 1963 the Veterans Administration (VA) hospital system decided to create artificial kidney units, or as they are now called, dialysis centers, in thirty hospitals around the United States. The VA system had many patients dying from chronic renal failure as a result of hypertension, diabetes, and injuries and was desperate to locate a technique that might help these patients.

VA patients were well suited to dialysis treatment, since many were permanently institutionalized with serious diseases or injuries that made it unlikely they would ever be discharged from the hospital. There were many patients readily available in a relatively small number of locations. This made it possible to bring the artificial kidney to the patients, rather than the patients to the artifical kidney. This was an especially important consideration for a treatment that physicians were beginning to realize required at least three sessions a week of four to five hours each to have any hope of efficacy.

The interest of the VA was crucial as a vehicle for disseminating Scribner's invention and the concept of using dialysis to treat chronic renal failure throughout the American hospital system. A large number of physicians receive their advanced training within the VA system and, thus, were exposed to Scribner's shunt and the concept of chronic hemodialysis early on in their careers.

By 1968 about 1,000 patients were receiving long-term renal dialysis for chronic renal failure in the United States (Rettig 1976; Russell 1979). A small number of physicians had acquired some experience with the treatment. And a small number of facilities capable of carrying out the procedure had been created.

It was about this time that the first of what eventually became a torrent of articles appeared discussing the ethical consequences of a shortage of dialysis machines available for those with chronic renal failure (Abram and Wadlington 1968; Beecher 1969; Rescher 1969). There were far fewer centers and doctors available to do the procedure then there were patients dying from chronic renal failure.

About 5,000 patients were dying each year in the United States from chronic renal failure. The solution of the problem of how to gain permanent access to the

circulatory system created a new problem of how to determine access to the small number of centers capable of performing the procedure.

Matters were made more complex by the fact that the answer to the question of whether long-term dialysis for chronic renal failure was safe and efficacious were slow in coming. Scribner initially obtained good results using his shunt on a fairly broad cross-section of patients with chronic renal failure. His initial success was so impressive that it became hard for him and other physicians to obtain funds for research on chronic hemodialysis since it looked as if chronic hemodialysis, had sprung into existence as a full-fledged medical cure.

But as the number of doctors and centers using the technique began to grow, physicians began to have trouble duplicating Scribner's low morbidity and mortality rates. Some thought the results of chronic hemodialysis were so poor that the procedure ought be abandoned. Others felt that chronic hemodialysis was still very experimental and ought only be allowed to spread slowly into the general hospital system.

By its very nature the effects of chronic hemodialysis on the human body were difficult to study. Long periods of time were required both to determine efficacy and to ascertain whether any adverse side effects might be associated with long-term exposure to hemodialysis.

After an initial period of success, many doctors became skeptical of the promise of chronic hemodialysis. But after a few more years, roughly by the mid-1960s, other centers began to achieve better success in their morbidity and mortality rates. However some hospitals continued to have patients who suffered many severe side effects or even died while on chronic hemodialysis. This mixed bag of results led to a dispute within nephrology as to what the proper course of action should be with respect to the expansion of dialysis services.

Matters were made even more contentious as a result of the emergence during the early 1960s of a new form of treatment for chronic renal failure—transplantation. Renal transplants from either living or cadaver sources were seen by some as less costly and more enhancing of a patient's quality of life than thrice-weekly dialysis treatments. Chronic hemodialysis was competing for the same therapeutic niche as kidney transplants, and each evolving treatment had its advocates and detractors.

The dispute over which technique was more efficacious, involving as it did the VA hospital system, caught the attention of federal officials. They needed to know if the VA was wasting its money on a losing form of treatment. The VA was also under increasing pressure to expand services, both within the VA system and in other federally funded health care programs to minimize the need to ration access to dialysis. The federal government created a commission headed by Dr. C. W. Gottschalk to examine the controversy over chronic hemodialysis.

The commission issued a report in 1967. The report gave a strong endorsement to both chronic dialysis and kidney transplantation. The report noted that,

> . . . transplantation and dialysis techniques are sufficiently perfected at present to warrant launching a national treatment program and urges this course of action. (Report of the Committee on Chronic Kidney Disease, 1967)

The committee was composed primarily of people who made their livings performing either dialysis or transplantation. So in one sense it is not surprising that the commission took the Solomonic course of weighing the available evidence and then deciding to bless both approaches to renal failure as therapies.

V. What Can the Philosophy of Science Learn from an Examination of Early Efforts to Treat Chronic Renal Failure?

The case of the evolution of a clinical treatment for chronic renal failure poses a number of challenges to existing models of conceptual change in the philosophy of science. Philosophers rarely acknowledge that, occasionally, disputes in science are resolved by procedural means. In the case of hemodialysis, a committee was formed, a study undertaken, a vote taken, and a conclusive finding was issued.

Using a committee to resolve a dispute is a long way from designing a crucial experiment to test conflicting hypotheses. But committees and other bureaucratic structures have important roles to play in determining the direction and course of inquiry in many areas of science (Englehardt and Caplan 1987)

Less dramatic but nonetheless of interest is the role played by practical success in determining the pace and course of scientific work. Deaths had a discouraging effect on the willingness of scientists to believe that long-term hemodialysis using a Scribner-Quinton shunt was a valid therapeutic approach. Theoretical questions about the degree to which a combination of a plastic shunt and plastic membrane could duplicate the function of the nephron of the kidney were almost irrelevant in understanding the evolution of clinical strategies for treating renal failure. What mattered was how many patients were alive and healthy and how many were not, after prolonged exposure to the artificial kidney.

The assessment of the ideas and hypotheses advanced in the pursuit of a treatment for chronic renal failure was complicated by the presence of another therapeutic option. The fact that two approaches to treatment were in competition had a very real impact on how the success rates of dialysis and transplantation were evaluated. As we shall shortly see, the competition between plausible research strategies for solving the problem of how to treat renal failure had a distinct impact on the composition of the subject pool that was afforded access to chronic hemodialysis and the interpretation of evidence concerning efficacy.

Of great import is the pattern of development manifest in the early history of chronic hemodialysis. Discovery in the biomedical realm is often only the first in a long sequence of events, not the final stage of a lengthy inquiry. Those who

discover new drugs, devices, or materials must convince their peers that they have found an answer to a problem. But the proof requires more than publication. It requires active promotion, an active interaction between doctor and invention, good results initially, good results in the long run, and results that are better than other available options.

Technological solutions, at least in the case of chronic hemodialysis, follow a course of evolution that moves from the recognition of a problem to the formulation of a solution to selling others on the merits of the purported solution. A discovery is almost always followed by a long period of what might best be termed "advertising" during which agnostics, skeptics, and devotees of alternative approaches must all be persuaded to accept the merits of the purported breakthrough (Banta 1984).

This phase is then followed by a stage that might be termed "acceptance," during which evidence of efficacy must be accumulated and evaluated. Sometimes formal certification of the sort that can best be provided by a blue-ribbon panel of experts is the only mechanism by which disputes concerning the acceptability of a new treatment can be resolved.

Philosophers of science have not given sufficient emphasis to the identification of the developmental phases that lead from discovery to acceptance. Discovery, even by recognized authorities in a given field, does not always lead to acceptance. Analyses of theoretical evolution must remain alert to the sequence of events following on the heels of a discovery, which may or may not result in acceptance.

VI. From Acceptance to Mastery

In 1968 about 1,000 Americans were receiving renal dialysis treatment. By 1978 more than 35,000 were having their lives extended by dialysis. And by 1988, more than 98,000 patients were receiving dialysis treatment (HCFA 1988).

These numbers raise a number of interesting and important questions relevant to understanding the evolution of theories in medicine. Why has the number of patients receiving dialysis continued to grow twenty years after the medical profession decreed that dialysis was in fact a legitimate form of medical therapy? What kinds of factors played a role in decisions made by physicians to control the numbers of persons with fatal forms of renal failure who had access to dialysis treatment?

Some of the variables influencing the rate of growth manifest by dialysis throughout the general population are easy to identify. The number of centers, kidney machines, and trained personnel available to deliver dialysis was much smaller in 1968 than was the case in 1978 or 1988. The cost of performing thrice-weekly regimens of dialysis, ranging from $20,000 to $30,000 per year, were

large enough to discourage some patients dying of renal failure from seeking care.

The growth in the number of patients receiving dialysis also reflects the fact that some persons who started dialysis in 1968 were still receiving care in 1988. The growth in the number of patients is accumulative, since the overall patient pool reflects both new patients added each year plus ongoing cases of renal failure from previous years.

But it is important to realize that the composition of the patient population receiving dialysis changed drastically from 1968 to 1988. In the late 1960s the majority of dialysis recipients were young, 25 to 45, middle or upper class, married males with no other significant illnesses. By 1988 the majority of patients being dialyzed were 45 years of age or older. Dialysis had been attempted on newborns as well as on those over 90. Current recipients included men and women from all walks of life. Many had signficant complicating illnesses such as diabetes, arthritis, alchoholism, depression, and even cancer.

As one physician observed in 1968,

> We had what was in many ways an idealized population. A large fraction of the patients were living in a productive period of their lives. They were young and had little else wrong with them. (Kolata 1980)

By 1988 the patient pool barely resembled that of this early period.

The most common reasons cited in the literature of medicine and the history of medicine for the change in the composition of the pool of patients receiving hemodialysis are money and bias. Some commentators argue that physicians were simply biased against those from backgrounds different then their own and when faced with a shortage of resources acted to penalize those they disliked (Fox and Swazey 1978; Plough 1986).

Others argue that it was the decision by the federal government to pay for the costs of dialysis therapy for all patients in renal failure in 1972 that opened the floodgates to this treatment modality. When the federal government created a special program, the End Stage Renal Dialysis Program, to cover nearly all of the costs of dialysis, money was no longer an obstacle to access.

Explanations such as these are likely to delight sociologists and historians who are sensitive to the nonepistemic, or external factors that drive the evolution of science (Englehardt and Caplan 1987). But, while doctors did show bias, especially with respect to race and sex, in their selection of potential recipients, and while money played an important role in enabling more patients to receive care then would have been possible without governmental assistance, there is more going on in the expansion of the dialysis patient pool than is captured by explanations of change confined to only prejudice, money, or both.

The easiest demonstration that more than money was involved in the sudden expansion of the pool of dialysis patients comes from the British experience with

renal dialysis. The United Kingdom had a national health insurance system in place that dated back to the end of the Second World War. Money was not an obstacle for offering dialysis to those with renal failure.

Yet, British nephrologists were as selective as their American counterparts in controlling the access of patients with renal failure to dialysis. During the 1960s four out of five potential candidates for dialysis were rejected. Patients were usually young, male, married, working, and homeowners. Yet by the 1980s the pool of patients receiving dialysis care had demonstrated enormous growth.

The explanation of the selective policies regarding access to renal dialysis that prevailed in the United States and England well into the 1970s lies in what are sometimes termed internal or epistemic considerations (Englehardt and Caplan 1987). Victor Parsons, a British nephrologist, puts his finger on the methodological considerations that influenced the selection of patients for dialysis in both countries:

> Individual desire to go on living or the desire to be treated was not considered. . . . very often the patients were unaware they were up for selection. This enabled the renal units to achieve high survival rates, and quite rightly since in the early stages it was important that the treatment should be seen in its best possible light. To have adopted a totally non-selective policy at the outset would have led the technique into disrepute as being nothing but a technical exercise in the prolongation of a very poor quality of life. (Parsons 1978)

Those involved with dialysis had to demonstrate both its safety and its efficacy. Moreover, they had to demonstrate its efficacy relative to an alternative therapy—renal transplants. The way to accomplish these goals was to utilize patients who would permit physicians to observe adverse side effects. It was also to use patients who were likely to respond well to the treatment. Those who were relatively well-off, who had no other disabling diseases, who were young, and who had supportive families were the most likely to fulfill the need to demonstrate efficacy, safety, and technical superiority over alternative approaches.

It is important to realize that selectivity in the pool of patients receiving dialysis remained a fact of life in both the United States and Britain long after the Gottschalk commission had declared renal dialysis to be a therapy and long after the American government had created a fund to pay for the costs of dialysis care. By the late 1960s doctors had learned to perform chronic renal dialysis with success. But part of the reason behind their success was the care with which patients were selected for treatment.

During the next twenty years nephrologists learned to utilize dialysis on a broad range of patients. They mastered the technique by treating the very young and the very old, those with many serious medical complications, and those whose psychosocial environment was less than optimal.

The process by which health care professionals learn to master a therapy

should be of great interest to those interested in theory change in the sciences. Long after a new innovation is recognized as therapeutic, sustained efforts are directed toward learning the proper management of the therapy across the entire spectrum of potential patients. Much the same process is currently underway with respect to cardiac transplants, liver transplants, balloon angioplasty, and lithotripsy. Competition and money, as well as prestige and concerns for safety and efficacy, all play roles in determining the boundaries of the patient population for which doctors believe a therapy is indicated.

VII. Forces Driving the Evolution of Experiments into Therapies

One of the most interesting questions to emerge from a consideration of the recent history of chronic hemodialysis is: Why did dialysis move so quickly from the status of experimentation to that of therapy? After all, despite the fact that dialysis was declared a therapy in 1967, it took another twenty years for physicians to feel comfortable enough with the technique to offer it to all persons suffering from renal failure.

The desire of biomedical scientists who do human experimentation to quickly shed the label of experimentation has interesting analogues in other areas of medical innovation. Those involved in attempting the first artificial heart implant and who conducted the first xenograft of a heart to a young infant were quick to declare their efforts therapeutic and nonexperimental (Caplan1985a, 1985b). The therapeutic status of these interventions was seen as established by the demonstration of the mere feasibility of the undertaking.

There are many reasons why those involved in the development of new medical interventions such as dialysis wish to dispose of the label "experimental" as soon as they can. Experimentation carries with it connotations of the unknown, the risky, and the especially dangerous. Talk of experimentation can make it difficult to recruit willing subjects. Such connotations are unfortunate since there are many experiments that are relatively safe and risk free, and many therapies that are precisely the opposite.

Another reason for the rapid transmutation of experiments into therapies is hope. Those who treat the sick and those who are sick or disabled naturally want to have a cure. Talk of "therapy" is far more conducive to optimism than is talk of "experimentation" or "research." Researchers involved in the development of new drugs to treat terminal cancers or to help those suffering from AIDS find it much easier to offer comfort to the dying using the language of therapy rather than research.

Another factor influencing the speed with which experimentation becomes therapy is the assignment of credit for discoveries. Few scientists or physicians get credit or public acclaim for being the first to conduct experiments. Credit goes to those who find cures, who discover therapies.

If the first use of an artificial kidney or heart is experimental, or, if the first baby born as a result of IVF constitutes a successful outcome of research, then others may try to claim credit for the first truly "successful" application of a new technology or technique. And as the long evolution of hemodialysis shows, there are many steps that must be made to move from discovery to mastery. The race in biomedicine for fame, fortune and celebrity goes to those who find cures. Priority is no small matter in a scientific world of fierce competition for grants, fame, and recognition.

There is another important force driving new techniques, drugs, and devices down the continuum from research to therapy—money. Third-party payers, whether public or private, do not want to pay for experimentation. Those giving grants for basic research do not want to fund therapy.

There are many reasons for physicians to push new treatments across the spectrum from discoveries to therapies. But as the history of chronic hemodialysis reveals, there are also reasons for wondering whether these two categories are adequate for understanding the evolution of treatments in medicine or products in other areas of applied science.

VIII. What Criteria Ought Govern the Language of Experimentation and Therapy?

It is interesting to see exactly how existing regulations governing human experimentation define research. The so-called Belmont Report, published in 1979, which played a key role in the formation of existing federal guidelines concerning human experimentation, used the following definitions:

> practice—"interventions designed solely to enhance the well-being of an individual patient that have a reasonable expectation of success."
>
> research—"an activity designed to test a hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge."

Existing regulations governing institutional review boards (IRBs) reflect the considerations raised in the Belmont report definitions. Research is defined as, "a systematic investigation designed to develop or contribute to generalizable knowledge."

These definitions place great weight on intent. If a biomedical scientist believes that what he or she is doing is done solely to help benefit a patient with some chance of success, then what is done is a part of practice. It is therapy. If the goal or intent is to produce generalizable knowledge, then what is done is research.

But these definitions leave too much to intentions. While the goals of therapy and research clearly are different, it is odd to make the distinction entirely contingent upon the aim of the health care professional. Even the most honest and forth-

right clinician is going to have a hard time describing what he or she is doing as research if it means adverse and often disastrous fiscal consequences for patients plus a loss of hope for those suffering from fatal illness.

Whatever the defining characteristics of research, they must go beyond the subjective intent of the health care provider or scientist. Two characteristics that would appear to be especially relevant are the state of knowledge prevailing about the underlying mechanisms or processes that produce a particular result, and the efficacy associated with a particular activity in terms of the probability that it will produce its intended outcome.

If a physician can produce a cure in a patient but does not have any idea why the cure comes about, then, in a key respect, the intervention is experimental. The reason this is so is that it may not be clear exactly what intervention or contributing factor is responsible for producing the outcome that is sought.

For example, dermatologists have long known that a combination of ultraviolet light and coal tar helps many persons suffering from psoriasis. The cure rate associated with this regimen is quite high. Nonetheless, physicians remain uncertain exactly what frequencies of ultraviolet light, what components of the coal tar and what combinations of light and coal tar, are responsible for symptomatic relief. The treatment is certainly useful. But, it is still experimental. Why it works is at least as relevant to the description of what dermatologists do as is the fact that it has benefits for those who receive the ministrations.

Nephrologists in the 1960s felt they had a treatment that could duplicate the function of the normal kidneys. But, in fact, it took twenty years of clinical and experimental research to establish the biochemical and biophysical similarities and differences between chronic hemodialysis and the naturally occurring process of filtration and osmosis in the kidney.

But theoretical knowledge is not sufficient in medicine for establishing a treatment as therapeutic. Interventions that fail to extend life or that have disastrous side effects are still seen as experimental, even if the underlying mechanisms of action are well understood.

Oncologists may describe various drugs as therapeutic for lung cancer, cancer of the pancreas, or cancer of the liver, but the fact is, no available drug regimens are efficacious against these forms of cancer. While an oncologist may believe he or she is providing therapy to those with cancers of this sort, they often refer to their efforts in talking to one another as experimentation.

Background knowledge concerning causal mechanisms and efficacy are both key factors that must be considered in assigning a particular intervention a place on the experimentation-to-therapy continuum. Intentions in and of themselves are not sufficient to distinguish research from therapy.

Unfortunately there is very little discussion of the degrees of efficacy and safety that ought constitute adequate evidence for establishing the therapeutic status of an intervention. And, as the history of chronic hemodialysis should make

plain, there are many opportunities presented for the drawing of lines on the path from discovery to mastery.

The problem becomes even more pressing when it is made clear how the provision of new treatments is closely linked to the need to establish therapeutic efficacy and safety, as well as to competitive and economic factors. Values and facts mix freely in fueling the course of thinking in clinical medicine. Those seeking examples of such interactions would be well advised to look in this domain of science. And those who would advance overarching theories to explain conceptual change in the sciences must look in this domain to see whether the theoretical and the applied are miscible to a degree compatible with a univocal approach to understanding scientific change.

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